REMARKS

Claims 1-23 are pending in this application. Claims 1-19 are rejected and claims 20-23 are withdrawn as being drawn to a non-elected invention. By the present amendment, claims 1, 3, 4, 6, 10, 11, 14, 15, 17, and 18 are amended; claims 2, 5, 9, 12, 13, 16, and 19-23 are hereby canceled without prejudice or disclaimer; and new claims 24 and 25 are hereby added. Support for the amendments and new claims are found in paragraphs 11, 63, 74-78 and elsewhere throughout the application. Accordingly, the amendments and new claims add no new matter.

Applicants wish to thank the Examiner for the telephone interview on September 5, 2007, during which the amendment to recite a method which employs a nucleic acid encoding a KChAP protein rather than a method which employs both a nucleic acid encoding a KChAP protein and the KChAP protein itself was discussed.

In view of the above-described amendments and following remarks, reconsideration of claims 1, 3, 4, 6-8, 10, 11, 14, 15, 17, and 18, and consideration of new claims 24 and 25 are hereby requested.

OBJECTIONS TO DRAWINGS

The specifciation/drawing have been amended to include sequence identifiers for the PIAS family proteins shown in Figure 10. The sequence listing has also been amended to include the sequences shown in Figure 10. In view of these amendments, applicants request the objection be withdrawn.

CLAIM OBJECTIONS

Claims 1-10 are objected to objected to as being incomplete. As mentioned above, the claims have been amended to recite a nucleic acid encoding a KChAp protein as discussed during the teleconference of September 5, 2007. (See above) In view of the amendments, applicants request that the objections be withdrawn.

CLAIM REJECTIONS-35 USC § 112-SECOND PARAGRAPH

Claims 1, 4, and 19 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claim 1 and 4 have been amended to recite that the method comprises delivering to and expressing in epithelial carcinoma, or prostate cancer or breast cancer cells, respectively, a

nucleic acid encoding KChAP protein. Applicants submit that claims 1 and 4 as amended recite all essential steps, and that the rejection should be withdrawn. Claim 19 has been canceled without prejudice or disclaimer rendering the rejection moot.

CLAIM REJECTIONS-35 USC § 112-WRITTEN DESCRIPTION

Claims 1-19 are rejected under 35 USC §112, first paragraph as failing to comply with the written description requirement. (See page 4 of the Office Action.). Claims 2, 5, 9, 12, 13, 16, and 19 have been canceled rendering the rejection of these claims moot. Claims 1, 4, and 11, as amended no longer recited a variant of the KChAP protein or a protein related to KChAP. Accordingly, applicants submit that claims 1, 4, and 11 and the claims that depend therefrom all meet the written description requirement of 35 USC §112.

CLAIM REJECTIONS-35 USC § 112 SCOPE OF ENABLEMENT

Claims 1-19 are rejected under 35 USC §112, first paragraph as failing to comply with the enablement requirement. (See page 6 of the Office Action.) Statements in the Office Action in support of the rejection include the following:

> Regarding the use of nude mice as the in vivo model of human cancer the prior art of Kerbel (Cancer & Metastasis Rev. 17:301-304, 1999) teaches that "Most transplantable tumor therapy experiments utilize ectopic (usually subcutaneous) injection and growth of the cells. The positive responses of such tumors to certain anti-cancer drugs or therapies have been questioned and at least in **some** cases it has been shown that orthotopically transplanted tumors do not necessarily recapitulate the 'encouraging' responses of their ectopically grown counterparts...The response to therapy of a single 'primary' (usually ectopic/subcutaneous) growing transplanted tumor mass is usually what is evaluated rather than that of distant metastases growing in visceral organs such as the brain lungs, or liver....there is clearly a need to place more emphasis on tumor models in which metastases are the primary target of therapy, and not just a transplanted 'primary' tumor." ...In the instant case Applicants have not utilized primary tumor cells and have further administered the cells hetertopically." (See page 9 of the Office Action.) (Emphasis added.)
>
> ...
> At the time of filing, the prior art taught the importance of orthotopic transplantation of tumor cells in developing animal models of tumor growth that accurately recapitulate the growth and metastases of the tumor in the original host mammal. Vieweg et al. (first column, p. 196; Cancer Investigation, 13(2) 193-201, 1995 disclose: "the site of tumor implantation can greatly influence biological properties and immunological response to treatment"....Hoffman

> (Invest. New Drugs 17:343-360, 1999) notes that currently used rodent tumor models, including transgenic tumor models, or subcutaneously-growing human tumors in immunodeficient mice, do not sufficiently represent clinical cancer, especially with regard to metastasis and drug sensitivity. (See page 10 of the Office Action.)(Emphasis added.)
>
> ...
>
> The instantly claimed methods rely on the activity of KChAP protein in cells to induced [sic] apoptosis. In a post-filing review of the role of K^+ channels in regulating tumor cell proliferation and apoptosis (Wang (Eur. J. Physiol . 448:274-286;2004), the author states "K^+ channels favor tumor proliferation, therefore, inhibition of K^+ channel function or down-regulation of K^+ channel expression should inhibit tumorigenesis...On the other hand, K^+ channels also promote apoptotic cell death...enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation. This apparent paradox confounds the manipulation of K^+ channel function and/or expression as an option for the treatment of cancers." (pp 281-282 bridging)(See page 10 of the Office Action.)

Claims 1, 4, and 11, as amended no longer recited a variant of the KChAP protein or a protein related to KChAP. Moreover, the present application provides evidence showing that the claimed methods promote apoptosis in prostate cancer cells, whether the cells are in a culture dish or in an animal tumor. (See paragraphs 106-108, 113, and 115 of the present application.) The present application provides evidence that increasing levels of KChAP in prostate cancer cells arrests cell cycling in these cells. (See paragraph 111) The present application also provides evidence that increasing levels of KChAP protein increases p53 levels in these cells, and that this increase is not dependent on K+ efflux. (See paragarphs 109 and 110.) The present application also provides evidence that a method which involves delivering and expressing nucleic acids that encode a KChAP protein into cells of prostate tumors that have been created by injecting prostate carcinoma cells that express either a wild-type or mutated p53 protein into nude mice suppressed growth or reduced the size of these tumors. (See paragraphs 114 and 116 of the present application.) Thus, the claimed treatment produced a meaningful benefit in theses animals.

In support of the rejection, the Office Action quoted statements from Kerbel (Cancer & Metastasis Rev. 17:301-304, 1999), Vieweg et al. (Cancer Investigation, 13(2) 193-201, 1995), Hoffman (Invest. New Drugs 17:343-360, 1999) and Wang (Eur. J. Physiol . 448:274-286;2004). (See above.) However, nowhere in any of these four (4) references is there any indication that the in vivo model used by applicants has not successfully been used and can not successfully be

used to identify proteins that enhance apoptosis of tumor cells in vitro or in vivo **AND** suppress growth of prostate tumors in vivo. Vieweg is a report that reviews and discusses "the concept and rationale for the use of cytokine-secreting tumor vaccines for the treatment of human malignancies". (See abstract of Vieweg.) Hence, the emphasis on using models that allow one to study immunological effects. Krebel and Hoffman are directed at identifying "improved" or "optimum" animal models for testing antitumor and antimetastatic drugs. (See title of Kerbel.) Hoffman in particular suggests that orthotic implantation of tumor fragments may be better particularly when evaluating the effect of a drug on metastasis. (See column 1 on page 345 of Hoffman."Thus the SOI models are a significant improvement allowing the full metastatic potential of human tumors to be expressed in a rodent model." Emphasis added.) While a nucleic acid which encodes a protein that increases apoptosis of tumor cells, suppresses growth of tumors, reduces the size of established tumors, and inhibits metastasis would be a particularly useful molecule for treating subjects with prostate or breast cancer, a nucleic acid encoding a protein that promotes less than all of these benefits is also of value..

Wang et al., a review article that recounts studies conducted to examine the role of potassium channels in tumor cell proliferation and tumor cell apoptosis, discusses but does not dispute or contradict the studies reported in the present application showing that increasing levels of KChAP protein in breast cancer and prostate cancer cells promotes apoptosis AND inhibits growth of prostate tumors. Applicants would like to point out that KChAP is potassium channel modulatory protein that interacts with and binds to many proteins that are not potassium channels. (See paragraph [0052] of the present application. Thus, the effect of KChAP on tumor growth in a subject may be independent of its effect on potassium efflux. Moreover, most of the Kv channels that are modulated by KChAP including Kv 1.4, 1.5, 2.1, 2.2, 4.2, 4.3, and the Kv beta subunits have not been identified by Wang as being involved in regulating cell proliferation. Finally, in the sentences immediately following those quoted in the Office Action, Wang et al. states that "Nonetheless, when used strategically, benefits may be attained. It is tempting to propose that K^+ channel blockers could be used in the early stage of carcinogenesis to prevent over-proliferation of tumour cells and K^+ channel openers might be employed in the late stage of carcinomas to kill the tumour cells. (see column 1, page 282 of Wang et al.). Thus, Wang et al. does not argue against using elevated levels of KChAP to treat subjects with tumors.

In view of the amendments to the claims, the guidance provided by the instant application showing that expression of a nucleic acid encoding KChAP can a) promote apoptosis of prostate

cancer cells in vitro and in vivo, b) arrest cell cycling, c) reduce the size or suppress the growth of prostate tumors in animals, and the absence of any statements in the Krebel, Vieweg, Hoffman, or Wang which negates these findings, applicants submit that claims 1, 4, and 11 and the claims that depend therefrom are enabled. Accordingly, applicants request withdrawal of the rejections.

Applicants submit that claims 1, 3, 4, 6-8, 10, 11, 14, 15, 17, and 18, as amended, and new claims 24 and 25 are now in condition for allowance. If the Examiner has any questions regarding the claims, he is encouraged to contact the undersigned at the phone number listed below.

Respectfully submitted,

Date: September 26, 2007

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